REMARKS

Claims 1 and 8-52 are pending in the present case. Claims 1 and 8-12 have been examined and stand rejected under 35 U.S.C. § 101, § 112, first and second paragraphs, and § 102(e). Each of these rejections is addressed below.

Request for Continued Prosecution Application (CPA) under 37 C.F.R. § 1.53(d)

The Office states that the request for a CPA under 37 C.F.R. § 1.53(d) is improper because the application does not meet the requirements of 37 C.F.R. § 1.53(d), namely, that the prior application of a CPA must be (1) *a utility* or plant *application that was filed under 35 U.S.C. § 111(a) before May 29, 2000*, (2) a design application, or (3) the national stage of an international application that was filed under 35 U.S.C. § 363 before May 29, 2000. Applicant respectfully points out that this application is a CPA of utility application, U.S.S.N. 09/456,693, filed on December 9, 1999 (i.e., a utility application that was filed under 35 U.S.C. § 111(a) before May 29, 2000). Therefore, Applicant's request for a CPA meets the requirements of 37 C.F.R. § 1.53(d)(1), and the present application should be treated as such.

Election of claims

Applicant affirms the election, with traverse, of Group I, claims 1 and 8-12. Applicant reserves the right to pursue all canceled subject matter in this or any currently

pending or future application.

Rejection of claims 1 and 8-12 under 35 U.S.C. § 101

Claims 1 and 8-12 stand rejected under 35 U.S.C. § 101 because, according to the Office, the claimed invention is not supported by either a specific asserted utility or a well established utility. The Office cites the Court in *Brenner v. Manson* as saying that an invention must have either an immediately apparent or fully disclosed "real world" utility. *Brenner v. Manson* 148 U.S.P.Q. 689 (1966). Applicant respectfully points out that both criteria are met in the present case.

First, the "specific asserted utility" of the presently claimed libraries is described at a number of sections in the specification. For example, on page 3, lines 11-13 of the specification it states, "These antibody mimics may be utilized for the purpose of designing proteins which are capable of binding to virtually any compound (for example, any protein) of interest." In addition, on page 13, lines 15-17, the specification states, "There are now described below exemplary fibronectin-based scaffolds and their use for identifying, selecting, and evolving novel binding proteins as well as their target ligands." Furthermore, on page 21, lines 1-6, under the heading "Use," the specification reads (emphasis added):

> The antibody mimics described herein may be evolved to bind any antigen of interest. These proteins have thermodynamic properties superior to those of natural antibodies and can be evolved rapidly in vitro. *Accordingly, these antibody mimics may be employed in place of antibodies in all areas in which antibodies are used, including in the research,*

therapeutic, and diagnostic fields.

In addition to these specified asserted uses for the presently claimed libraries, an example of a library that "was subjected to selection for binding to TNF-α" is provided on page 27, line 5 to page 28, line 4. Such a fibronectin scaffold-based library was, in fact, demonstrated to contain useful TNF-α binding proteins. As evidence of this, Applicant has attached PCT publication number WO 02/032925, filed on October 16, 2001 (Exhibit A), a later filed application in this family. This PCT application provides experimental data demonstrating that several TNF-α binding proteins were identified using fibronectin scaffold-based libraries and the same screen for TNF-α binders that is described in the present application. These experiments clearly demonstrate that the libraries of the present invention are indeed useful -- and for the very utilities that are "fully disclosed" in the present specification.

Applicant further points out that the usefulness of a library, such as the one claimed in the present invention, as a screening tool is also "immediately apparent" to one skilled in the art. A library that is generally useful for screening for protein-protein interactions will be recognized for its broad use and applicability by any skilled artisan. The libraries of the present invention are particularly useful for a variety of protein-protein interaction screens and therefore cannot be limited to one specific screen for one specific product. However, an example using TNF-α is provided (page 27, line 5 to page 28, line 4) to illustrate one of the many uses of the claimed invention. In fact, it is the

broad applicability of the library claimed in the present case that makes the invention particularly useful. Applicant asserts that the use of the library of the claimed invention is therefore not only fully disclosed but also immediately apparent, and the § 101 rejection should be withdrawn.

The Office also states that claims 1 and 8-12 are rejected under 35 U.S.C. § 112, first paragraph because, according to the Office, the claimed invention is not supported by a specific utility, and therefore one skilled in the art would not know how to use the claimed invention. Based on the arguments presented above, Applicant asserts that the claimed invention *is* supported by a specific utility and that one skilled in the art would know how to use the invention based on general knowledge in the art as well as the specific examples described in the specification. This rejection should also be withdrawn.

Rejection of claims 1 and 8-12 under 35 U.S.C. § 112, first paragraph

Claims 1 and 8-12 stand further rejected under 35 U.S.C. § 112, first paragraph, for failure to convey possession of the claimed invention at the time the application was filed. The Office states that the specification fails to provide an adequate written description for the criteria by which an amino acid is defined as basic, neutral, or acidic. The Office also states that the single disclosed motif, Serine-Glycine-Glutamate, does not appear to be within the scope of the disclosed genus because serine is not an art-

recognized basic residue and glutamate is not an art-recognized acidic residue. Applicant respectfully traverses this rejection.

First, Applicant notes that the rejection based on the lack of adequate written description for the criteria by which an amino acid is defined applies only to claim 10. On this basis alone, the rejection as applied to claims 1, 8, 9, 11, and 12 should be withdrawn.

Moreover, with respect to the assertion that the specification fails to provide an adequate written description for the criteria by which an amino acid is defined as basic, neutral, or acidic, Applicant notes that such criteria need not be spelled out in the present specification as they are well known in the art. Amino acids are typically grouped into three categories: polar, hydrophilic amino acids; nonpolar, hydrophobic amino acids; and "special" amino acids, based on the characteristics of their variable side chains or "R" groups. The polar, hydrophilic amino acids can be further separated depending on whether they are ionizable or they are charged at neutral pH. There are four highly ionized amino acids which include arginine, lysine, aspartic acid, and glutamic acid (glutamate). The pK of the R group for each of these amino acids indicates whether they are basic (e.g., Arg, pK=12.5, Lys, pK=10.8) or acidic (Asp, pK=3.9, Glu, pK=4.1). The nonpolar, hydrophobic amino acids have side chains that are hydrophobic and are located in the interior of proteins. These amino acids are considered neutral because they are electrically neutral at physiological pH. As the definitions of basic, neutral, and acidic

amino acids can be found in almost any basic biochemistry or molecular biology textbook (e.g. *Molecular Cell Biology*, Harvey Lodish et al., W.H. Freeman and Co., 2003), they need not be spelled out in Applicant's specification to satisfy the written description requirement. This portion of the rejection may be withdrawn.

The Office also rejects claims 1 and 8-12 under 35 U.S.C. § 112, first paragraph based on the assertion that serine is not an art-recognized basic residue and glutamate is not an art-recognized acidic residue. As an initial matter, Applicant first points out that this rejection should apply only to claim 11, a claim that recites the limitation that the integrin-binding domain of a ^{10}Fn3-based protein be replaced with an amino acid sequence comprising serine-glycine-glutamate. Moreover, as stated above, glutamate is a known acidic amino acid with a pK of 4.1. And serine falls under a class of amino acids which are considered polar but are weakly ionizable, containing an aliphatic hydroxyl group which makes it very hydrophobic and reactive. The R group for serine has a pK value of approximately 13, making this amino acid basic.[1] Accordingly, serine and glutamate do indeed constitute art recognized basic and acidic amino acids, respectively, and this basis for the rejection should be withdrawn.

In addition, Applicant points out that claim 11 is fully supported by a written description in the present specification at page 28, lines 6-11. There, Applicant describes ^{10}Fn3-based proteins possessing a serine-glycine-glutamate sequence in place of the

[1] pK values cited herein were obtained from the following web site: http://www.indstate.edu/thcme/mwking/amino-acids.html.

naturally-occurring integrin binding domain. In view of this description, claim 11 satisfies the written description requirement, regardless of whether serine is an art recognized basic residue or glutamate is an art recognized acidic residue. This portion of the §112 rejection should be withdrawn.

Finally, the Office states that the specification fails to provide a written description for a library of "scaffold-based proteins," disclosing instead a "fibronectin-based scaffold." As amended claim 1 now reads:

> A library of proteins derived from the tenth module of the human fibronectin type III domain (^{10}Fn3) and having at least three randomized loops, said library comprising proteins being characterized by their ability to bind to compounds that are not bound by said human fibronectin type III domain and wherein said binding ability results from said randomization of said at least three loops.

Amended claim 1 no longer refers to a "scaffold-based" protein, and this portion of the rejection is now moot.

Rejection of claims 1 and 8-12 under 35 U.S.C. § 112, second paragraph

Claims 1 and 8-12 stand further rejected under 35 U.S.C. § 112, second paragraph, for failing to distinctly claim the subject matter of the claimed invention. The Office states that the phrase "scaffold-based protein" is unclear and that the metes and bounds of the basic-neutral-acidic residues are also unclear.

As described above, claim 1 has been amended so that it no longer contains the phrase "scaffold-based protein." This portion of the rejection is therefore moot.

Furthermore, also as described above, the metes and bounds of basic, neutral, and acidic residues are clearly known in the art. Accordingly, the rejection as applied to this term may be withdrawn.

Rejection of claims 1 and 8-12 under 35 U.S.C. § 102(e)

Claims 1 and 8-12 also stand rejected under 35 U.S.C. § 102(e) as being anticipated by Koide (Publication No. 2002/0019517). This rejection is respectfully traversed.

To support a rejection of a claim under § 102, a single prior art reference must describe all of the elements and limitations of the rejected claim. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001, 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991).

The current claims require a library of proteins, the members of which include human ^{10}Fn3-based proteins having *at least three randomized loops* that result in compound binding activity. Koide does not disclose such a library.

The Koide reference teaches the use of fibronectin-based monobodies asserted to be capable of binding to different structures. The Office relies on paragraphs 0022-0028 of the published application as support for the present rejection. These paragraphs state that "one or more of the monobody loop region sequences of the Fn3 polypeptide vary by deletion, insertion, or replacement...." These paragraphs also list which amino acids

make up the AB, BC, CD, DE, EF, and FG loops. Despite this general description of the amino acid sequences that make up the Fn3 loops, there is no disclosure in the reference of ^{10}Fn3-based proteins with *at least three randomized loops*. Rather, Koide discloses only monobodies in which *one or two loops* have been varied and suggests that variation of additional sequences would destabilize the entire protein.

In particular examples, at paragraph 0137, Koide states, "The first library was constructed of the Fn3 domain displayed on the surface of the MB phage in which seven residues (77-83) in the FG loop (FIG. 4D) were randomized....Another library was also generated in which the BC loop (residues 26-20) was also randomized." Example VI discloses nucleic acid phage display libraries having mutations in the FG loop and the BC loop. Tables 3 and 4 of Koide show the sequences of specific monobodies isolated from Koide Library 2, which contains "variegated" residues in the BC loop, and Koide Library 4, which contains "variegated" residues in each of the BC and the FG loops. Thus, as indicated in these sections, Koide always teaches randomization of only one or two loops, and never discloses randomization of all three loops.

In addition, not only does Koide fail to disclose ^{10}Fn3-based proteins with at least three randomized loops, Koide also teaches away from the variation of additional loop sequences. In particular, in Example XVII, Koide provides results from measurements of stability for one of their monobodies (Ubi4-K) which was isolated from a library of monobodies having five randomized residues in each of the BC and FG loops (paragraph

0194 of the published application). Koide states that the "mutations in the two loops *certainly decreased the stability* of Ubi4-K relative to wild-type Fn3." From this teaching, one skilled in the art would be led away from the introduction of additional mutations into the protein, for example, into a third loop, as these mutations would be expected to further destabilize the monobody protein. As such, not only does Koide fail to teach a ^{10}Fn3-based protein having *at least three randomized loops*, this reference also teaches away from the production of this type of protein due to stability considerations. None of claims 1 or 8-12 can therefore be anticipated by Koide, and the § 102(e) rejection should be withdrawn.

CONCLUSION

Applicant submits that the claims are now in condition for allowance, and such action is respectfully requested.

Applicant notes that the Form PTO-1449 that was submitted with an Information Disclosure Statement filed on April 11, 2002 has not been initialed and returned, and hereby requests that it be initialed and returned with the next Office action.

Enclosed are a Petition to extend the period for replying to the Office action for three months, to and including September 13, 2003, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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